REMARKS

Claims 4-8, 10, and 11 are currently pending for examination, with amendments to claims 4 and 5 as set forth above.

Specifically, claims 4 and 5 have been amended to recite that the polypeptide contains "neither a repeat site nor any portion of an F-spondin domain . . . ." Claim 5 has also been amended to recite that the polynucleotide contains "neither a nucleotide sequence encoding a repeat domain nor a nucleotide sequence encoding any portion of an F-spondin domain . . . ." Support for these amendments can be found in the original claims 4 and 5, and in the specification, at least at page 4, lines 24-25 and page 25, lines 12-14.

Claim 4 has been amended to replace the recitation of a "CR-50 antibody recognition site of Reelin protein" with the phrase "region of Reelin protein recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2." Claim 5 has been amended to replace the recitation of "CR-50 antibody" with the phrase "monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2." Support for these amendments can be found in the specification, at least at page 4, lines 11-12.

Additional informalities in claim 5 have been corrected.

Thus, the claims are fully supported by the application as originally filed and the amendments add no new matter.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Written Description

At page 3 of the Action, the Examiner maintained the rejection of claims 4-8, 10, and 11 under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention." *Action* at page 3. Applicants respectfully traverse this rejection.

According to the Examiner, adequate written description support for the claimed polynucleotide genus would include **either** "recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, **or** of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus." *Id.* at page 4 (emphasis added). Despite this statement, the Examiner required the first of these conditions, alleging that "the instant disclosure of a single polypeptide . . . and a single nucleic acid encoding it . . . does not adequately support the scope of the claimed genus." *Id.* at page 3.

In repeating the rejection, the Examiner did not address Applicants' arguments, presented in an Amendment dated March 1, 2004, and entered upon filing of a Request for Continued Examination on April 30, 2004, that the claims recite specific structural features that adequately support the claimed genus.

Claims 4 and 5 themselves precisely define the genus by suitable structural and functional features. In claim 4, the encoded polypeptide either (a) is derived from a mouse Reelin polypeptide, whose sequence is known, or (b) contains SEQ ID NO: 2, or, alternatively, contains a deletion, substitution, or addition variation (or is encoded by a degenerative nucleic acid sequence) of the antibody recognition regions specified in (a) or (b). In all cases, the encoded polypeptide contains no portion of an F-spondin domain or a repeat site and binds to the monoclonal antibody. Sequences falling within the scope of claim 4 are limited by both the short length of the unique segment of Reelin in which the epitope is found, amino acids 191-500 (see Fig. 4 of Tissir et al., Nat. Rev. Neurosci., 4:496-505, 2003, submitted with the Amendment

dated March 1, 2004), and the ability to bind to the monoclonal antibody. Similarly, claim 5 is limited to a polynucleotide containing SEQ ID NO: 1 or its deletion, substitution, or addition variants, provided that the variation encodes a polypeptide that binds to the monoclonal antibody. Again, the genus is structurally well defined. "[I]t may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'" *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

Applicants therefore maintain that the specification provides an adequate written description to support the scope of amended claims 4 and 5 and claims 8-11, which depend therefrom. Reconsideration and withdrawal of the instant rejection is respectfully requested.

Enablement

At page 5 of the Action, the Examiner maintained the rejection of claims 4-8, 10, and 11 under 35 U.S.C. § 112, first paragraph, alleging that "the specification, while being enabling for the polynucleotide of SEQ ID NO:1, does not reasonably provide enablement for" the other claims, and "does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." *Action* at page 5. Specifically, the Examiner alleged that "the claims are directed to polynucleotides encoding peptides with greater than single amino acid substitutions, deletions and insertions and to partial peptide fragments which bind CR-50 antibody[, y]et the specification fails to teach alternative sequences." *Id.* at page 7. Accordingly, the Examiner alleged that one skilled in the art could not "practice the invention as broadly claimed without undue experimentation." *Id.* at page 5. Applicants respectfully traverse the rejection.

In repeating the rejection, the Examiner did not address Applicants' arguments, presented in the Amendment dated March 1, 2004, and entered upon filing of a Request for Continued Examination on April 30, 2004, that modifying a polypeptide and testing it for specific binding activity do not involve undue experimentation.

As discussed above, one well-defined group of molecules (claim 4) contains polynucleotides that encode polypeptides that are derived from a mouse Reelin polypeptide, or their deletion, substitution, or addition variants, and that bind to the monoclonal antibody. In another group of molecules (claim 5), the polynucleotides include deletions, substitutions, or additions of one or more nucleotides of SEQ ID NO: 1. SEQ ID NO: 1 contains 351 nucleotides. The section of Reelin containing the monoclonal antibody epitope contains 310 amino acids. Thus the alternative sequences potentially included within the claimed genus are clearly defined. Moreover, the claims are limited to resulting polypeptides that bind to the monoclonal antibody.

It would be a matter of routine experimentation, and not undue experimentation, for one of ordinary skill in the art to modify the known sequences to yield polypeptides that bind to the antibody while lacking any portion of an F-spondin domain or a repeat site. Sequence modification techniques are conventional. Screening tests for antibody binding are well known and have repeatedly been held by courts to be routine. Furthermore, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (internal citation omitted). In fact, the Office's own 1999 Interim Written Description Guidelines state, in Example 16, that "the level of skill and knowledge in the art of antibodies . . . was such that production of antibodies against a well-characterized antigen was conventional. This is a mature technology

where the level of skill is high and advanced." The Examiner herself acknowledges the "high skill in the art of making antibodies specific to various peptide regions . . . ." *Action* at page 17. Likewise, production of and screening tests for antigens that bind to a known antibody are conventional. Additionally, the specification teaches, at least in Examples 2 and 3, how to detect, express, and purify polypeptides that bind to the monoclonal antibody.

Regarding claims 10 and 11, the Examiner alleged that "the specification fails to teach such suitable compositions for stimulating the assembly of Reelin protein molecules or for providing a pharmaceutical for diagnosis or treatment of diseases resulting from abnormally positioned neurons." *Action* at page 7. Applicants respectfully traverse.

The specification explicitly describes, at least at page 11, line 24, through page 12, line 5, how the homophilic interaction of Reelin molecules may be mediated by the CR-50 epitope region, i.e., by a region that binds to a monoclonal antibody binding to SEQ ID NO: 2. Regarding claim 11, the specification indicates that those in the art recognize that "Reelin controls neuronal migration and positioning," and that "CR-50 antibody has neutralizing activity of Reelin functions." Specification at page 2, line 20 to page 13, line 17.

Applicants therefore maintain that the specification fully enables amended claims 4 and 5 and their dependent claims 8-11. Reconsideration and withdrawal of the foregoing 35 U.S.C. § 112, first paragraph, enablement rejections is respectfully requested.

Public Availability of Antibody

At page 10 of the Action, the Examiner maintained the rejection of claims 4-8, 10, and 11 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner stated that:

> the specification is non-enabling with respect to [antibody CR-50 binding] because there is insufficient assurance that the antibody can be

> reproducibly isolated and/or is publicly available. While the antibody is recognized in the prior art, the antibody is required to make and use the invention as claimed. In particular, the peptides are in part defined by their testing positive for CR-50 immunoreactivity.

Action at page 10. Applicants respectfully traverse this rejection.

Solely to expedite prosecution and without acquiescing to the Examiner's contentions, Applicants have amended Claims 4 and 5 to specify that the antibody is "a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2." CR-50 is such an antibody. According to the Manual of Patent Examining Procedure § 2404.02, "Applicant may show that a deposit is not necessary even though specific biological materials are required to practice the invention if those biological materials can be made or isolated without undue experimentation." Applicants' specification teaches the nucleotide and polypeptide sequences of the specific region of the Reelin protein that is recognized by the monoclonal antibody. One of ordinary skill in the art would readily be able to prepare an antibody that recognizes this epitope using standard molecular biological techniques. In fact, courts have expressly recognized that "[t]he details of [the hybridoma] process are well known," and that "screening methods used to identify necessary characteristics, including affinity, of the monoclonal antibodies used in the invention were known in the art [in 1978]." *Hybritech Inc., v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Furthermore, as discussed above, the Office's 1999 Interim Written Description Guidelines indicate in Example 16 that "production of antibodies against a well-characterized antigen was conventional. This is a mature technology where the level of skill is high and advanced." A monoclonal antibody to SEQ ID NO: 2 can be produced and isolated using conventional techniques that do not require undue experimentation, and a deposit is therefore not necessary to comply with the enablement requirement.

Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION UNDER 35 U.S.C. § 102

At page 13 of the Action, the Examiner maintained the rejection of claims 4-8, 10, and 11 under 35 U.S.C. § 102(b) as allegedly being anticipated by de Bergeyck et al., J. Neurosci. Methods 82:17-24, 1988 ("de Bergeyck"). *Action* at page 13. de Bergeyck discloses "[p]rotein H (for 'hinge')[, which] corresponds to residues 164-496 of the reelin sequence." de Bergeyck at page 22. The Examiner stated that, while protein H "only comprises a portion (27 amino acids) of the F-spondin domain, such does not correspond to having an F-spondin domain." *Action* at page 14. The Examiner further stated that protein H may be considered to be "a mutant [polypeptide] lacking any of an F-spondin domain while containing a 27 amino acid addition." *Id.*

Claims 4 and 5, as amended, specify that the polypeptide does not contain "any portion of an F-spondin domain." As conceded by the Examiner, protein H of de Bergeyck contains 27 amino acids of the F-spondin domain. That is, de Bergeyck discloses a polypeptide containing a portion of the F-spondin domain. Hence de Bergeyck does not disclose all of the limitations of claims 4 and 5 and cannot anticipate the claims.

Furthermore, although the "comprising" language encompasses polypeptides containing additional amino acids to those in the monoclonal antibody binding region, such polypeptides cannot contain a portion of the F-spondin sequence. That is, polypeptides within the claim scope do not contain an amino acid sequence recognizable as a portion of the F-spondin sequence. The H peptide contains a 27-amino acid sequence that corresponds directly to a 27-amino acid sequence of the F-spondin domain. In the Examiner's example, "a mutant lacking any of an F-spondin domain while containing a 27 amino acid addition" that makes up a partial sequence of

the F-spondin domain could not be considered to lack any portion of an F-spondin domain. The Examiner admits as much, stating that "de Bergeyck et al. does not teach a specific peptide immunogen consisting of the CR-50 epitope region and thus containing none of the F-spondin domain." *Action* at page 16.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

REJECTION UNDER 35 U.S.C. § 103

At page 15 of the Action, the Examiner rejected claims 4-8, 10, and 11 under 35 U.S.C. § 103 as allegedly being unpatentable over de Bergeyck; Nakajima et al., PNAS 94:8196-8201, 1997 ("Nakajima"); and Miyata et al., J. Neurosci. 17:3599-3609, 1997 ("Miyata"). *Action* at page 15. The Examiner stated that:

> one of ordinary skill in the art would be motivated to produce a peptide consisting of the CR-50 epitope peptide to make CR-50 epitope specific antibodies capable of blocking the noted reeler phenotype as suggested by Nakajima and Miyata. One of skill in the art would expect success using such techniques given the high skill in the art of making antibodies specific to various peptide regions and the teachings of Miyata and Nakajima that it is the CR-50 epitope that directs the reeler phenotype. The antibody so generated would provide for the advantages of CR-50 in functional testing within the in vitro and in vivo model systems. Thus, the cumulative reference teaching render the claimed invention obvious to one of skill in the art.

Id. at 17. Thus, the Examiner asserts that the reference teachings suggest producing a CR-50 epitope peptide in order to make an antibody that binds to the CR-50 epitope of Reelin protein, which is capable of blocking the Reeler phenotype. Applicants respectfully traverse this rejection.

de Bergeyck is directed to identifying antibodies to Reelin protein that are different from the CR-50 antibody. After discussing the CR-50 antibody and its epitope, de Bergeyck states:

"As reelin is such a large molecule, the understanding of its function would presumably benefit from the availability of additional antibodies directed against different portions of the molecule." *Id.* at pages 17-18. To obtain these antibodies, de Bergeyck creates peptides and "fusion proteins used for immunization or epitope localization." *Id.* at page 18, Fig. 1. The only uses disclosed for the peptides are to generate additional antibodies and to locate epitopes on Reelin that bind to those antibodies. Because de Bergeyck is concerned with identifying antibodies other than CR-50, peptides lacking the F-spondin domain or repeat sites are not employed.

Miyata does not cure the defect of de Bergeyck. Miyata discloses the inhibitory effect of the CR-50 monoclonal antibody on the regulation of Purkinje cell alignment by Reelin. Miyata at pages 3607-08. Additional in vivo functional experimentation with the CR-50 antibody is proposed to further elucidate the role of Reelin in developing brains. *Id.* at page 3609. Unlike de Bergeyck, in which peptides are used to produce and characterize novel antibodies, Miyata is concerned only with using a known antibody. Miyata does not suggest producing additional antibodies, and there is no apparent advantage to producing an additional monoclonal antibody that recognizes the same epitope as an existing monoclonal antibody. Thus the reason de Bergeyck provides for producing an isolated epitope peptide is not relevant to the teachings of Miyata, and there is no motivation to combine the references as suggested by the Examiner. The combination of references, therefore, neither suggests nor teaches producing a polynucleotide encoding a polypeptide recognized by a monoclonal antibody to Reelin protein that binds SEQ ID NO:2 and contains neither a repeat site nor any portion of an F-spondin domain, as recited in the present claims.

Nor does Nakajima cure the defects of de Bergeyck and Miyata. Nakajima discloses the potential role of the CR-50 epitope on Reelin in hippocampus development, based on the ability

of CR-50 to disrupt organized development of the hippocampus in vivo. Nakajima at abstract, page 8196. Nakajima also suggests "[f]urther precise mapping and analysis of the CR-50 epitope region . . . to formulate a hypothesis on the mode of interaction between Reelin and other molecules." *Id.* at page 8200. Like Miyata, Nakajima is concerned only with using a known antibody. Nakajima does not propose novel antibodies to Reelin, and there is no apparent advantage to producing an additional monoclonal antibody that recognizes the same epitope as an existing monoclonal antibody. Without a suggestion to generate novel antibodies in Nakajima, there is no motivation to modify the methods of de Bergeyck to isolate a peptide that binds to the CR-50 antibody. Thus, there is no motivation to combine the two references or to produce a polynucleotide encoding a polypeptide that is recognized by a monoclonal antibody to Reelin protein that binds to SEQ ID NO: 2, and that contains neither a repeat site nor any portion of an F-spondin domain, as recited in the present claims.

None of the three references, alone or in combination, teaches or suggests the inventions of claims 4-8, 10, and 11. Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner does not consider the application to be in condition for allowance, Applicants request that the Examiner call the undersigned ((650) 849-6611) to arrange an interview prior to taking action.

Please grant any further extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Dated: November 10, 2004

By: _____
Jennifer L. Elliott
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